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Epidemiological Aspects of Respiratory Mycotic Infections[1]

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INTRODUCTION

Epidemiology of the mycotic agents must derive its information from a variety of disciplines concerned with the study of human disease: mycology, ecology, epizootiology, immunology, vital statistics, pathology, and clinical impressions. The present discussion will deal with the diseases caused by *Histoplasma capsulatum*, *Coccidioides immitis*, *Cryptococcus neoformans*, and *Blastomyces dermatitidis*, though the fact is acknowledged that important respiratory infections are occasionally induced by other fungi.

HISTOPLASMOSIS

Histoplasmosis, or *Histoplasma*, appears to be worldwide in occurrence: from Vera Cruz to Viet Nam (72), from Peoria to Peru, and from Texas to Tanganyika (5). In some instances, this seems unexpected, as with the isolation of *Histoplasma* from soil near Bologna, Italy (110), or diagnosis of the disease in two British subjects resident on Cyprus (114). The results of worldwide surveys (28) have made the expanding histoplasmal vistas less surprising.

Nevertheless, a striking incidence of clinical cases and of skin reactivity to histoplasmin is noted in the midwestern United States. Furcolow (37) has demonstrated that in the region of Kansas City, Mo., the percentage of reactors to histoplasmin progressively increases so that, by age 20 to 25 years, 70 to 80% of the population (males and females) have had their contact with *Histoplasma*. It has become necessary to focus attention on the urban incidence of this disease which has in the past been considered rural.

Association of *Histoplasma* and histoplasmosis with avian habitats and with bats has been an exciting development in epidemiological knowledge of histoplasmosis (3, 40). We had an opportunity to learn of the association with bats when, in early 1956, we isolated *H. capsulatum* from two of three graduate students who had developed severe pneumonitis shortly after returning to Berkeley from Nayarit in western Mexico. We were also able to isolate *H. capsulatum* from the guano-laden soil from the bat cave visited by the students. Significantly, *H. capsulatum* has been isolated from the tissues of bats in Panama and Colombia (71, 97). Emmons et al. (33) have isolated *Histoplasma* from 16% of 300 bats obtained in Frio Cave near Concan (Uvalde County), Tex., not far from Utopia. This may help to explain the relatively high histoplasmin reactivity in that area, which overlaps the coccidioidal endemic zone.

Outbreaks or epidemics have intensified interest in the avian and chiropteran habitats (38, 40, 44*a*). These outbreaks may in part be due to a greater number of infectious microconidia produced in the presence of bird (i.e., starling) manure (102). However, it should be recalled that Procknow et al. (86) demonstrated experimental respiratory pathogenicity of the tuberculate chlamydospore, although the majority were 5 μ or less in diameter. The airborne infectivity of *H. capsulatum* has recently been emphasized by Murray and Howard (77), who urge precaution against laboratory infection. It is ironic that attempts to clear the site of origin of an epidemic resulted in still another outbreak (74).

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It is clear from the usual symptomatic cases and the usual residua (e.g., pulmonary calcification) from subclinical or mild cases that histoplasmosis is primarily a respiratory disease. Primary cutaneous infection has been a rarity (119). Furcolow (38) estimates that 500,000 persons a year acquire the infection. Over 99% of these will recover; many (perhaps half) will have had no awareness of the infection. Some will clear completely, but many (perhaps 70%) will develop the "primary complex" which may later calcify (101, 116).

It is estimated that in about 1,000 persons each year (i.e., 1 in 500 infections) the infection will disseminate from the lungs and, if untreated, may be fatal. This is said to occur more commonly in young children, in old age, and in association with certain intercurrent diseases (Hodgkin's disease and leukemia). Owing to the frequency of association with the latter diseases, *Histoplasma* can partially be classed as an "opportunistic fungus" with *C. neoformans*.

A chronic cavitary histoplasmosis sometimes develops, especially in older patients, and resembles the prolonged, troublesome, chronic pulmonary tuberculosis (39). Indeed, it has been estimated that 3,000 to 4,000 such cases are admitted annually to tuberculosis sanitoria for antimycobacterial therapy (38). Although this form, as well as the acute disseminated form, benefits from amphotericin therapy, it is felt that prolonged intermittent therapy may be needed in chronic cavitary patients (36). The latter appear somehow to be immunologically defective, although apparently capable of reacting to histoplasmin.

Symptomatic histoplasmosis occurs with lower frequency in females (representing less than one-third of cases), though they are infected with equal frequency (38). Negroes incur both acute disseminated and chronic cavitary disease with less frequency than Caucasians—certainly different from the picture in coccidioidomycosis.

The question of reinfection is not clearly resolved as yet. Schwarz and Baum (94) have argued that the chronic cavitary histoplasmosis represents exogenous reinfection. This is based on the observation of old calcified lesions in persons harboring *H. capsulatum* in younger lesions, i.e., with caseation. Presumably, the latter developed from (exogenous) reinfection superimposed on the healed primary infection. Others support this view (38), though, inasmuch as the chronic cavitary disease may last for many years, lesions with greatly varying age could be expected in an individual, as for example the fibrocaseo-calcific coccidioidal lesions (23, 49). A disease such as histoplasmosis with organisms sequestered in reticuloendothelial cells could perhaps be expected to relapse in some instances, as in brucellosis. However, that exogenous reinfection may occur with massive exposure to *Histoplasma* spores must certainly be entertained (37).

It has become clear that even dissemination of *Histoplasma* outside the lungs during the primary illness need not lead to a dismal prognosis. This may also be true of primary coccidioidomycosis (21). Christie (20) reported recovery of three infants (less than 6 months of age) despite hepatosplenomegaly and isolation of *Histoplasma* from the marrow. Support for this has come from the demonstration of splenic calcification (9, 115). Indeed, in areas endemic for histoplasmosis, e.g., Cincinnati, Ohio, careful routine autopsy studies have shown close to 50% of persons with splenic calcifications of probable histoplasmal origin (115). Arrest of the infection even in metapulmonary foci is the rule.

Control and prevention are important but still unsolved problems in histoplasmosis. Decreasing exposure to the airborne spores seems to be difficult to attain. Three individuals became infected despite the wearing of respirators used in mining (38), suggesting that prevention by this means was elusive. Of course, by now, cave explorers should be apprised of the hazard of their occupation. On the other hand, occurrence of cases in endemic areas can be expected during dry, dusty periods (38), although the seasonal incidence of histoplasmosis has not been emphasized as it has for coccidioidomycosis (106). Should effective immunization methods be developed, their application would be a massive undertaking if the estimate of 500,000 infections per year is precise.

COCCIDIOIDOMYCOSIS

In coccidioidomycosis, no characteristic specific lesion develops in bone as in syphilis or leprosy, which allows speculation on the existence of the disease during antiquity in the endemic areas of the Western Hemisphere. Today over 50,000 persons per year may have an active encounter with *Coccidioides immitis*, 25,000 of which will be clinically apparent (79). The conformity of endemic areas and the Lower Sonoran Life Zone is an arresting feature, though still unexplained. The endemic areas are being more closely defined. For example, Mayorga-P (73) has summarized six human and eight animal cases of coccidioidomycosis in Central America, thus extending an earlier report (19). Gonzalez-Ochoa (41) cites occurrence of 15 cases in the city of Torreón, Mexico, which has nearby a bat cave in which histoplasmosis was acquired (51), thus adding to

the endemic overlap of these two diseases as indicated by Ajello (3).

Reports of cases and skin test reactivity from Europe deserve close attention (8, 70). The purported demonstration of coccidioidomycosis in a rabbit in Hungary (55) is not acceptable from the published account. Doubtless, infections do occur outside the endemic areas with the greater ease of intercontinental movement (57). Harrell and Honeycutt (47) have referred to coccidioidomycosis as "a traveling fungus disease." Numerous instances have been cited of transmission of the fungus and acquisition of infection outside the endemic areas. Albert and Sellers (6) found 24 case reports of fomite transmission; however, only 9 of these had mycological confirmation of the diagnosis. Such fomite transmission has also occurred nearer the endemic areas by means of cotton bolls (105), relics or topsoil from old Indian campsites (81, 122), or from a plaster cast covering a purulent draining coccidioidal lesion (27). Some 200 or more probable cases, 59 of which were proved, have been acquired in the laboratory (53).

Concern has often been generated regarding the possibility of contagiousness, despite reassurances that it is highly unlikely (35, 54, 107). It is of interest that *C. immitis* in granulomatous pulmonary lesions was found in an infant monkey housed with its mother which had an experimentally induced purulent draining lesion of the forearm (18). The nearest to human contagion was the case reported by Wilson et al. (127), in which a lesion occurred in the injured finger of a man engaged in embalming the body of a person dead with disseminated coccidioidomycosis.

The yearly numbers of cases of coccidioidomycosis reported in California over the past 6 years were as follows: 1960, 268; 1961, 211; 1962, 260; 1963, 368; 1964, 272; 1965, 295 (112, 112*a*). There is, however, some doubt as to the completeness of case reporting. In any event, these figures are enriched by such outbreaks as that involving 26 persons (mostly children) in Canoga Park in February and March of 1965 (121), an almost perennial occurrence in the state (24, 27, 52, 84, 89, 120).

Coccidioidomycosis is usually a pulmonary disease, but there have now been reported 14 cases of primary cutaneous infection (42, 47, 63, 78, 109, 120, 127, 129, 131). Twelve of these healed uneventfully. One developed an underlying osseous lesion necessitating removal of bone, but thereafter fared well (78). One developed severe coccidioidal meningitis (129). The latter may necessitate some reservations about the essential benignity of the primary cutaneous inoculation. In this connection, it was found that, of 14 mice inoculated subcutaneously with *C. immitis*, all remained well, though 2 had demonstrable *C. immitis* in the viscera when killed 3 months later (81). There continues to be an impression that coccidioidal infection is handled better by children, but there is great need for precise information on this. The contribution of children to coccidioidal morbidity and mortality is sizable. In recent years, children have, in some studies, constituted about 7% of nonmeningitic dissemination undergoing amphotericin therapy, and 10 to 15% of those with meningitis (C. E. Smith, *unpublished data*).

The immunological bases for the greater resistance of females to dissemination or the greater *tendency* for Negroes and Filipinos to disseminate are unknown. One cannot generalize by saying "dark-skinned" races, because Huntington's (50) studies have indicated that Mexicans did not differ markedly from Caucasians in incidence of fatal coccidioidomycosis.

Three laboratory reinfections have been recorded (78, 107, 109), two of which were by percutaneous route. Nevertheless, true reinfections have not been documented in a natural setting. Reactivity to coccidioidin in a *healthy* subject continues to denote resistance to reinfection. But, in some recent studies, there has been reported a declining coccidioidin reactivity among certain groups, a finding of unknown significance (58, 60).

As susceptible subjects enter the endemic areas, the various forms of coccidioidal infection continue to be recognized. Pulmonary cavities, though relatively benign, may pose serious surgical problems. However, they are not comparable to the chronic pulmonary-cavitary histoplasmosis with its dismal outlook. Meningitis remains a threat, especially to Caucasian patients. It has even developed *during* amphotericin therapy. Although there is reason for optimism with the advent of amphotericin therapy, some cases may require intermittent therapy indefinitely.

Control and prevention remain goals. Improvement in chemotherapy or refinement of immunization procedures, or both, are needed. We can do little about the weather, and, as the dry, dusty summer approaches, we can again anticipate an increase in infections (106).

CRYPTOCOCCOSIS

Cryptococcus neoformans has been shown by Staib (111) to survive at least 1 year in dried bird manure or sand. This is a significant epidemiological attribute of an organism found worldwide and not known to produce a morphological spore form. The demonstration of a possible

selective effect of creatinine for *C. neoformans* is a fascinating addition to our knowledge of this organism and has already been employed in developing a selective medium (98).

Pigeon dung was incriminated as a ready source of *C. neoformans* by Emmons (30) in 1954. Since that time, it has become a popular, though often retrospective, question of the medical history to ascertain whether a patient with diagnosed cryptococcosis has been around pigeons or their roosting places. Probably no such *clear-cut* association has been established in the majority of cases. In a study conducted in New York, N. Y., Littman and Schneierson (67) showed that urban deposits of pigeon manure harbor *C. neoformans*. Halde and Fraher (45) have recently isolated *C. neoformans* from 1 of 10 specimens of pigeon dung collected in San Francisco, Calif.; Procknow et al. (85) succeeded in Chicago, Ill., and Partridge and Winner (82) in London. Littman et al. (66) recently showed that pigeons *can* be infected systemically with *C. neoformans* administered by the intracerebral route and inferred that these birds may themselves harbor the organism found in their excreta. It is attractive to ascribe infection to airborne cryptococci originating in desiccated dung. Littman (65) has described a resident physician who developed cryptococcal meningitis possibly as a result of exposure to an air-conditioner heavily contaminated with pigeon excreta. Procknow et al. (85) also present a compelling picture of such exposure for their patient. However, other instances of infection are not so directly referable to pigeon excreta.

Despite the emphatic and classical association with meningitis or meningoencephalitis, there is increasing reason to believe on clinical grounds, too, that cryptococcosis is primarily a pulmonary infection. Cavitary cryptococcosis (64, 123) and solid pulmonary lesions (113, 123, 124) alone or with other disseminated lesions may be found. Appearance of lesions in the skin, bones, or other tissues after resolution of primary pulmonary disease could be expected, as with other systemic mycoses. Some supportive evidence was provided by demonstrating infection of mice with airborne *C. neoformans* (103).

The experimental induction of disseminated cryptococcosis by feeding about 100 million (10^8) yeast cells to Marmoset monkeys is also of interest (118). Although the dose appears large, it is of interest that lesions were observed in a mesenteric lymph node, the brain, and myocardium. *C. neoformans* was cultured from meninges, brain, liver, and spleen, but none was evident in the gastrointestinal mucosa. Thus, penetration of the gut wall by cryptococci either swallowed directly or after being swept from th tracheobronchial tree suggests another means fo dissemination.

It is not possible at present to determine the frequency of subclinical cryptococcosis. The worldwide distribution of cases and the isolation of this yeast from natural sites, including urban, suggest a ubiquity. This is strengthened by the frequent association of cryptococcal disease with lymphomas and hematopoietic or other disorders, suggesting higher exposure rates than would be deduced from the incidence in otherwise healthy persons (56, 65, 88). Among these are the immunologically impaired states such as Hodgkins disease, Boeck's sarcoid, or thymoma and myasthenia gravis (90). The defect may be not only cellular, but concerned also with nullifying an inhibitory action of human serum on *C. neoformans* (10, 43). Abrahams (1) has approached this problem experimentally by demonstrating that mice with induced lymphomas had greater cryptococcal proliferation in liver and spleen, but apparently not in the brain, as compared with controls.

There has been no apparent racial predilection of cryptococcosis. More males are found with the disease than are females. It is predominantly a disease of adults, as suggested by the reporting of fewer than 50 cases in the under-15-year age group by 1963 (100). It is likely that this represents incomplete reporting or missed diagnoses. Nevertheless, the same shortcomings exist in connection with the reporting of adult cases, and it appears that children constitute less than an expected representation among clinical cryptococcosis.

It is of course redundant by now to plead for improved means of detecting past or current cryptococcal infection in hopes of ascertaining the prevalence of the disease. The recent efforts of Salvin and Smith (92) and Bennett and coworkers (14) have provided skin test antigens which may prove useful (75). It is possible that patients with active cryptococcosis (with or without serious intercurrent disease) will not respond to skin test antigens. The long persistence of cryptococcal polysaccharide has been shown in the circulation of animals (13). It is perhaps worth repeating that skin test antigens may well demonstrate valid and meaningful reactions in the general population, but such reactivity may be lacking in the active case, where, instead, one should attempt to demonstrate the circulating antigen (15*a*). An alternate approach can be suggested for exploration: peripheral-blood lymphocytes from persons with prior or current cryptococcal infection may respond in vitro to cryptococcal antigen by (blastoid) transformation

and mitosis. Thus, although humoral antibodies and dermal sensitivity have not been regularly useful, the circulating lymphocyte may be.

The prefix *crypto* thus continues to be an appropriate one, since much of the epidemiology remains obscure.

NORTH AMERICAN BLASTOMYCOSIS

Until the recent descriptions by Emmons et al. (34) of two cases of blastomycosis originating on the African continent, this disease appeared limited to the western hemisphere. Indeed, the occurrence of this disease had usually been more narrowly ascribed to the patient's presence in the eastern half of the United States [notwithstanding the reports of cases of "blastomycosis" in Spain (75) and Hungary (62), which deserved further supporting evidence]. A recent review of 198 cases of blastomycosis observed in Veterans Administration hospitals noted that the highest incidence was found in the southeastern United States (15). The unpublished report of Casad, Sorensen, Waldmand, and Levan has shown that, of 28 cases observed in Veterans Administration hospitals in California, all had probably acquired the disease elsewhere. There is a rough but broad conformity between areas of endemicity of histoplasmosis and blastomycosis extending along the Mississippi Valley. Because of this overlap, it would be cautious of the geographic pathologist to recall that in some specimens of tissue large cells of *H. capsulatum* or *H. duboisii* may resemble *Blastomyces dermatitidis*, and that small cell forms of the latter may resemble *H. capsulatum*. One should strive to fulfill Emmons' criterion, i.e., that *multinucleate* budding cells distinguish *B. dermatitidis* (32).

The usual manifestations of blastomycosis are related to lesions of the lungs or skin, though bones and urinary tract may be involved in a high proportion of cases. While acknowledging occurrence of documented cutaneous blastomycosis, Schwarz and Baum (93) provided cogent arguments for believing that blastomycosis generally commences as a respiratory infection which can be followed by dispersion to all organ systems.

Furthermore, the Veterans Administration study showed that farmers and laborers whose occupations brought them into relatively close contact with soil represented 50% of the total of their patients. The earlier reported single isolation of *B. dermatitidis* from the soil (25) has now received the desired and needed repetition (25*a*), though there does not appear to be a specific association with a peculiar soil site. Blastomycosis in dogs (87) or a horse (12) is suggestive of possible association of the organism with soil. Yet, blastomycosis in a sea lion which had spent 6 years in the Chicago zoo merely emphasized the question of the locus of this fungus in nature (126). An epidemic involving 10 patients in Pitt County, N. C. (108), was thoroughly investigated, but its source was not established. In this instance, however, it was not an explosive episode, since onset of the disease extended over a 5-month period (October, 1953, to March, 1954), and no single point of origin might be expected to seed the community over that time.

It was noted (108) that occurrence of these cases over the winter months was the expected for systemic blastomycosis as noted earlier by D. S. Martin. Clear-cut association of incidence with climatic conditions or season has not otherwise been obvious.

The North Carolina epidemic was noteworthy in yet another respect: the age span of the patients was 5 months to 77 years, but 7 of the 10 patients were under 16 years of age. This appears exceptional in that the peak incidence of reported blastomycosis has been between 30 and 40 years of age, though many occur also during the preceding decade of life (93).

The overwhelming predominance of cases of blastomycosis has been in males. Whether this indicates greater resistance of females, greater exposure of males through occupation, or a combination of both, has not been clarified by skin testing procedures which have proved useful in histoplasmosis and coccidioidomycosis. Use of the *Blastomyces* polysaccharide of Knight and Marcus (29, 59) gave skin reactions in about 1% of naval recruits, 20% of whom reacted to histoplasmin.

Reliable skin test information may also contribute information relative to resistance to reinfection in those persons who have recovered from an earlier bout with the fungus.

CROSS-IMMUNITY

The obvious overlapping of endemic areas, e.g., of blastomycosis and histoplasmosis, as well as migration of persons from areas endemic for histoplasmosis to those where *Coccidioides* abounds, has offered ample opportunity for exposure to at least two of these respiratory fungi. Despite this, consecutive or concurrent infections by two of these agents have only rarely been reported. In one person who had had evident blastomycosis for 9 years, both *H. capsulatum* and *B. dermatitidis* were demonstrated postmortem by culture and histopathological means (61). Six other cases of coexistent histoplasmal and blastomycotic lesions have been reported

(7, 16). Concurrent pulmonary histoplasmosis and coccidioidomycosis was reported by Perry et al. (83). Is the rarity of these cases suggestive of cross-protection? Certainly there is serological overlap of these three organisms.

Some measure of cross-protection has been shown in mice previously infected with *B. dermatitidis* or *H. capsulatum* and challenged with the heterologous organism (91, 96). In our own studies, still in a preliminary stage (80), we have compared mice inoculated subcutaneously with 100 viable arthrospores of *C. immitis* (nonlethal by this route) or 5,000 yeast cells of *H. capsulatum*. They were challenged 7 weeks later by intranasal and intraperitoneal administration of 100 to 5,000 *C. immitis* arthrospores. Prior infection with *C. immitis* protected against both intraperitoneal and intranasal challenge, whereas prior inoculation with *Histoplasma* did not protect against intranasal challenge, though it was effective against intraperitoneal challenge. In another experiment, 10^5 and 10^7 yeast cells of *H. capsulatum* were used as challenge doses by both intravenous and intraperitoneal routes in animals preinoculated subcutaneously as before. The larger (10^7) dose given intravenously proved lethal in 1 week in both *Histoplasma*- and *Coccidioides*-vaccinated animals, as well as in normal controls. Adequate evaluation of experimental histoplasmosis and its immunology may require a wait of several months for expression of mortality effects (44).

We await with interest, then, further studies in humans as well as in experimental hosts on the role of prior experience with a respiratory mycosis and the outcome of a subsequent exposure to a different organism.

CHEMOTHERAPY

There can be little doubt about the altered "epidemiology" of the mycotic diseases as a result of improved chemotherapy (48). For example, the outcome of both cryptococcal and coccidioidal meningitis, formerly regularly fatal, has been markedly affected by the introduction of amphotericin therapy (17, 128). Although many of these patients may require intermittent lifetime therapy, because amphotericin does not kill all the fungus cells, they perhaps can be kept from the rolls of mycotic mortality. There are equally encouraging indications regarding blastomycosis and histoplasmosis (95), though not all are willing to accept the impression of Baum and Schwarz "that North American blastomycosis is almost a conquered disease" (11). The true impact of newer chemotherapy on these diseases is difficult to assess precisely. Furcolow (36) was able to show the marked benefit (60% increase in survival) of treatment of disseminated and chronic pulmonary histoplasmosis, although it is difficult to obtain and match an untreated group of patients. In disseminated coccidioidomycosis, the beneficial effects of amphotericin are clearly evident in individual cases, but this form of the disease had 50% survival without therapy. The exact effects on chronic disseminated disease with single metapulmonary foci, as in the bones, remains to be evaluated.

As indicated before, there is need for more precise and inclusive reporting of infectious diseases. Some method is needed which will provide confidence that the reported cases reflect a closer approximation of true incidence.

SUMMARY

Four fungi pathogenic for man by the respiratory route have been discussed. *C. neoformans* and *H. capsulatum* are found worldwide, though the latter is confined to broad endemic areas. *B. dermatitidis* and *C. immitis* are geographically more restricted. Outbreaks of histoplasmosis and coccidioidomycosis associated with a dusty venture indicate that the respective fungi occur in particularly dense numbers in specific loci. The ease and extent of travel have brought the need for awareness of these diseases in places where they are not customarily seen. Cryptococcosis, thought possibly related to contaminated pigeon excreta, is being recognized increasingly as a disease outside the central nervous system. Blastomycosis is a disease of unknown incidence. *B. dermatitidis* has been isolated from the soil, but no specific distinguishing characteristics of these sites are apparent. The extent of occurrence of cryptococcosis or blastomycosis as benign or subclinical entities, as well as whether reinfection occurs, remains to be learned. Histoplasmosis is often linked to deposits of bird or bat manure. The disease appears to be contracted by several hundred thousand persons a year, usually with little disability. Its effects may be serious in young children, and, in older persons, a debilitating, possibly reinfection, form is seen. Coccidioidomycosis is usually benign but may be severe, especially in the Negro and Filipino. Resistance to reinfection is the rule in those who have once successfully coped with this disease. Rare cases of dual infection by these respiratory fungi have been reported. However, whether cross-immunity occurs in humans is unresolved. Chemotherapy has certainly altered the course of these diseases, but the overall quantitative influence on mortality is undefined.

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